A Placebo-Controlled Double Blind Trial of Etanercept for the Cancer Anorexia/Weight Loss Syndrome

Results From N00C1 From The North Central Cancer Treatment Group

Jatoi A, Dakhil SR, Nguyen PL, Sloan JA, Kugler JW, Rowland KM Jr, Soori GS, Wender DB, Fitch TR, Novotny PJ, Loprinzi CL.

Cancer. 2007 Sep 15;110(6):1396-403

Prepared by: Teri Tien
Presented: October 30, 2007, Journal Rounds on the Tertiary Palliative Care Unit, Grey Nuns Hospital.

BACKGROUND. Tumor necrosis factor-a (TNF-a) is a putative mediator of the cancer anorexia/weight loss syndrome. The current study was designed to determine whether etanercept (a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75-kilodalton TNF receptor linked to the Fc portion of human immunoglobulin [Ig] G1) could palliate this syndrome.
METHODS. A total of 63 evaluable patients were randomly assigned to receive either etanercept at a dose of 25 mg subcutaneously twice weekly versus a comparably administered placebo. All patients had an incurable malignancy, acknowledged loss of weight and/or appetite as a concern, and reported a weight loss of >2.27 kg over 2 months and/or a daily intake of <20 calories/kg body weight.
RESULTS. Over time, weight gain was found to be minimal in both treatment arms; no patient gained >= 10% of their baseline weight. Previously validated appetite questionnaires revealed negligible improvements in both treatment arms. The median survival was also comparable (175 days vs 148 days in etanercept-treated and placebo-exposed patients, respectively; P 5.82). Finally, preliminary data regarding adverse events demonstrated that patients treated with etanercept had higher rates of neurotoxicity (29% vs 0%) but lower rates of anemia (0% vs 19%) and thrombocytopenia (0% vs 14%). Infection rates were negligible in both groups. Genotyping for TNF-a-238 and TNF-a-308 polymorphisms revealed no clinical significance for these genotypes, except for a preliminary association between presence of the 2238 G/A genotype and relatively less favourable survival.
CONCLUSIONS. Etanercept, as prescribed in the current trial, does not appear to palliate the cancer anorexia/weight loss syndrome in patients with advanced disease. Cancer 2007;110:1396–403. ┌ 2007 American Cancer Society. KEYWORDS: cancer, etanercept, anorexia/weight loss syndrome, tumor necrosis factor-a, survival

Strengths:

- Intriguing example of rational drug design/use, using a commercially available preparation.
- Commented on good effect in mouse models.
- Relevant to our sample population:
- Adults with tissue proven malignancy, with documented weight loss, where the patient perceived weight loss as a problem.
- Randomized, double-blind, placebo controlled.

Weaknesses:

- Small sample size of 63 patients.
- No comment on allocation concealment.
- High drop-out rate.
    - No mention of how these drop-outs were handled in the statistical analysis.
    - No mention of intention-to-treat.
- Weight gain of 10% was judged to be a "treatment success." Analysis was using 2-tailed test. Why did they use discrete analysis techniques on what is normally considered continuous data?
- Results not able to reach statistical significance.

Relevance to Palliative Care: This study was unable to show an improvement in weight in anorexic/cachectic cancer patients treated with etanercept. The study is an interesting exploration of the anorexic process in a clinical population. However, the mechanism for weight loss is multifactorial and TNFa is not the only cytokine involved. On a more practical note, how accessible would monoclonal antibodies be for our population, were they to show an effect? The syndrome continues to be a common problem for which there are limited treatment options.